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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/708,952	04/02/2004	**Itzhak Bentwich**	050992.0301.00USCP	2951

37808 7590 12/30/2008

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
12/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/708,952	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18,22,23 and 25-28* is/are pending in the application.

4a) Of the above claim(s) *17,23 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16, 18,22,25, 26, and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004 and 22 May 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that applicant elected SEQ ID NO: 14051 in the reply filed on 6/18/07 with traverse. Furthermore, applicant elected without traverse group I, claims 16, 18, 19 and 21-23, in the reply filed on 9/19/07 is acknowledged.

Claims 17, 23, and 27, as well as the subject matter of claim 16 that is not directed to SEQ ID NO: 14051 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/18/07.

It is noted that applicant has added claims 25-28. Claim 27 is withdrawn as being directed to a non-elected invention. Therefore, claims 16, 18, 22, 25, 26, and 28 are examined herein, wherein claim 16 is examined to the extent to which it is directed to the elected invention.

Applicant's amendments and/or arguments filed 5/21/08, with respect to the rejection(s) of claim(s) under 35 USC 112, 2nd paragraph, 35 USC 112, 1st paragraph (new matter), 35 USC 102, and double patenting (except for 10/536,560) have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, the rejections below are pending and upon further consideration, a new ground(s) of rejection is made in view of the instant claim amendments.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 5/21/08 has been considered by the examiner.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).
The disclosure of the prior-filed applications fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

No support could be found in each of the prior-filed applications for an isolated nucleic acid identical in scope to instant claim 16, wherein SEQ ID NO: 399738 comprises the nucleic acid and the nucleic acid comprises SEQ ID NO: 14051 or a DNA encoding SEQ ID NO: 14051, or a sequence at least 80% identical to SEQ ID NO:

14051 or the DNA encoding SEQ ID NO: 14051, or the complement of SEQ ID NO: 14051, the DNA encoding SEQ ID NO: 14051, or any sequence that is at least 80% identical to either. It is noted that SEQ ID NO: 399738 is 7500 nucleotides in length. Therefore, the claims embrace every possible sequence that comprises SEQ ID NO: 14051, which is 22 nucleotides in length, and is up to 7500 nucleotides in length comprised within SEQ ID NO: 399738, as well as a DNA encoding each of the multitude of sequences, as well as any sequence that is at least 80% identical with any of the above mentioned sequences, as well as the complement of any of the above mentioned sequences. Support is not evident in each of the priority documents for the instant genus.

Therefore, the instant claims are accorded an effective filing date of 4/2/04, the filing date of the instant application. Should applicant disagree, applicant is encouraged to point out with particularity by page and line number where such support might exist for each claim limitation in each of the priority documents.

Claim Rejections - 35 USC § 101 and 112, First Paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 18, 22, 25, 26, and 28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility.

The claims are drawn to an isolated nucleic acid wherein SEQ ID NO: 399738 comprises the nucleic acid and the nucleic acid comprises SEQ ID NO: 14051; a DNA encoding SEQ ID NO: 14051; a sequence of any length that is at least 80% identical to SEQ ID NO: 14051 or a DNA encoding SEQ ID NO: 14051; and the complement of SEQ ID NO: 14051, a DNA encoding SEQ ID NO: 14051, or a sequence of any length that is at least 80% identical to either. Also claimed are vectors and probes comprising the nucleic acid.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation (see paragraph [0024]).

The specification discloses that "The present invention relates to a group of bioinformatically detectable novel viral oligonucleotides and to a group of bioinformatically detectable novel human oligonucleotides associated with viral infections, both are identified here as Genomic Address Messenger or GAM oligonucleotides. All of which are believed to be related to the micro RNA (miRNA) group of oligonucleotides" (see paragraphs [0022] and [0023]).

The specification discloses that "Additionally, the present invention relates to a novel group of bioinformatically detectable viral regulatory RNA oligonucleotides, which repress expression of viral target genes, by means of complementary hybridization to binding sites in untranslated regions of these viral target genes. It is believed that this novel group of viral oligonucleotides represents a pervasive novel internal viral regulation mechanism, and therefore knowledge of this novel group of viral oligonucleotides may be useful in preventing and treating viral diseases. " (see paragraph [0035]).

The specification discloses that bioinformatically detectable oligonucleotides have a sequence selected from the group consisting of SEQ ID NOs: 1-14456" (see paragraph [0054].

The specification discloses that GAMs represent precursor miRNAs or miRNA-like sequences encoded by a bacterial and/or human genome. Such sequences are predicted to have a hairpin like structure and to give rise to short, ~22-nt RNAs, which presumably provide gene repression activity.

The specification teaches how to detect and validate the expression of potential GAMs in cells. The specification discloses that GAM genes encode GAM precursor RNAs, which have structural similarities to miRNA genes. The specification teaches that the GAM precursors look like miRNA genes because they don't encode a protein and they have two-dimensional hairpin like structure, which is typical of RNA encoded by miRNA genes (see paragraph [0084]).

However, the specification provides no evidence for these assertions. Moreover, the specification discloses a multitude of sequences that have similar structural characteristics such as secondary hairpin folding to MIR precursor hairpins. However, the specification does not provide any evidence for a utility of the instantly recited sequences, SEQ ID NOs: 399738 and 14051. Applicant is broadly asserting a utility for a multitude of sequences based on miRNA-like structure.

Indeed, the asserted utility of these and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (Nature Genetics, 2006, 38: S14-S19)(cited and of record on the PTO-892 mailed on 11/21/07) state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5′ end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA

sequence requires analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences. There is no evidence verifying the expression of instant SEQ ID NO: 399738 comprising SEQ ID NO: 14051 in any cell line much less a human cell line or that its expression or absence thereof has been correlated any disease, bacterial or otherwise, or trait.

Further, Applicant has not provided evidence that instant sequences are up or down regulated in any cell or tissue, animal or bacteria, or plays any role in the predisposition of human or mammalian cells to infection.

Applicant's asserted utility appears to be based only on the predicted structure and sequence complementarity of sequences meeting the criteria of "GAM" sequences and on various reports in the prior art describing various genes and their correlation to diseases. From this, Applicant appears to extrapolate and thereby assert that inhibiting or somehow altering a target gene is beneficial, and that because the instant sequences have a predicted miRNA-like precursor structure and a sequence that is complementarity to some target sequence, it plays a role in inhibiting a target gene and treating a disease.

However, this assertion is not credible. While sequences within SEQ ID NO: 399738 may have complementarity to a gene, applicant has not presented any

evidence or established any nexus that SEQ ID NO: 399738 or sequences therein do target and/or inhibit a specific gene, much less that the expression or inhibition of expression of the instant sequences may be used to prevent or treat a disease associated with a target sequence. The asserted utility is speculative.

The specification does not establish a nexus between any particular disease state, bacterial process, or host cell process, and an altered level or form of the claimed sequences that would enable one of skill to use the instant sequences, or sequences meeting the broad instantly recited structural limitations, to achieve a beneficial effect.

In addition to the bioinformatically predicted utility, described above, the specification generally asserts that Genomic Address Messenger sequences may be used in various ways. However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial.

For example, the specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel oligonucleotides of the present invention and bacterial diseases, for disease diagnosis and prevention purposes, and for monitoring disease progress.

This asserted utility is neither specific nor substantial. Since the same can be done with any polynucleotide, the asserted utility is not specific. Also, because the

specification does not disclose any specific function for SEQ ID NO: 399738, it is unclear how or why one of skill in the art would use the information obtained by measuring SEQ ID NO: 399738 expression for any particular purpose aside from general research. Further, since applicant does not identify whether abnormal SEQ ID NO: 399738 expression is causally related to any disease or condition, or whether abnormal SEQ ID NO: 399738 (e.g., a polymorphism) predisposes anyone to any disease or condition such as infection, the only recognizable utility of diagnostic probes is as tools for scientific research, and with no indication that anything useful will be discovered. Therefore, the asserted utility is not substantial since the application provides no teaching regarding how to use the probes or expression data for any practical purpose beyond the art-recognized methods of gene expression analysis.

Accordingly, polynucleotide probes derived from the instant invention are simply research intermediates that may help scientists isolate the gene and conduct further experimentation. Such probes can only be used to detect or amplify the genetic material having the same structure as the probes themselves. The probes would provide no immediate, real-world information about the overall structure or function of the underlying gene, for example, aside from its expression patterns.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO: 399738, much less every possible fragment within SEQ ID NO: 399738 that comprises SEQ ID NO: 14051, DNA encoding each possible sequence, any length of sequence that is at least 80% identical to any of the sequences, or the complement of any of the sequences have any specific biological function. No evidence

or information is found either in the specification or the prior art linking SEQ ID NO: 399738 or the huge genus of sequence embraced by the instant claims with the modulation of any bacterial or mammalian gene or with the conditions that render cells or hosts susceptible to any bacterial infection, for example. No convincing evidence is found teaching any biological function for SEQ ID NO: 399738 at all. In fact, no evidence is found suggesting or stating that SEQ ID NO: 399738 has been made, isolated, cloned, detected, expressed, or even analyzed in a living cell *in vitro* or *in vivo*.

In summary, no biological or biochemical function has been assigned to SEQ ID NO: 399738 or sequences meeting the instant structural limitations, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to an miRNA precursor based on folding and have some direct or indirect relation to bacterial disease and/or life cycle.

Thus, Applicant has not demonstrated that SEQ ID NO: 399738 or sequences meeting the instant structural limitations may be used in any mode of therapy or as a general means to define and treat bacterial infections.

Thus, the proposed utility of SEQ ID NO: 399738 or sequences meeting the instant structural limitations as a therapeutic target or agent, or material resource for preparing diagnostic probes, vectors, a host cells, are simply starting points for further research and investigation into potential practical uses of the claimed polynucleotide.

Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until

> a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> …a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific, substantial, or credible utility for SEQ ID NO: 399738, much less other sequences meeting the instant structural limitations or any of the RNA equivalents or complements of SEQ ID NO: 399738. No target gene has been conclusively identified nor has any evidence been presented linking SEQ ID NO: 399738 or fragments thereof with any target gene, bacterial disease or infection, biological function or disorder. A credible, specific, and substantial nexus has not been established.

***

Claims 16, 18, 22, 25, 26, and 28 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Response to applicant's arguments

Applicant argues that the current application discloses a large number of nucleic acid sequences and provides that each of the disclosed nucleic acids may be used to target and modulate expression of specific gene transcripts. Applicant asserts that the claimed miRNA-related sequences specifically target mRNA transcripts of the target gene NP_039906.1. However, this asserted utility is merely speculated and has not been reduced to practice. The claimed sequences have structural similarity to known miRNA molecules. Applicant is basing the asserted utility upon structural similarities rather than upon any known activity of the instant sequences. miRNA sequences are not fully complementary to the target. Mere structural similarity is not sufficient support to establish utility for the instant sequences, lacking any evidence to the contrary. Furthermore, the scope of the claims is not supported by the asserted utility, as the specification does not disclose a utility for such a huge genus of sequences that embrace any nucleic acid comprised within SEQ ID NO: 399738, which is 7500 nucleotides in length, that comprises SEQ ID NO: 14051, which is 22 nucleotides in length. Therefore, the claims embrace any sequence within the 7500-mer that comprises the 22-mer, as well as a DNA encoding any of the sequences of this huge genus, as well as any sequence of any length that is at least 80% identical to any sequence of the huge genus or any DNA encoding any of the sequences, as well as the complement of any sequence of the huge genus, of any DNA encoding any of the sequences, or any of the sequences that are at least 80% identical. Applicant has not established a utility for the breadth of the sequences claimed.

Applicant argues that the instant sequences may be used to bind and regulate mRNA transcripts of NP_039906.1 and that ebv-miR-BART3 is known to be expressed and that this microRNA may play a particularly important role during the EBV infection of epithelial cells. Applicant sets forth that accordingly, ebv-miR-BART3 expression could be modulated in vitro to affect viral titer during EBV lytic replication. Applicant has set forth an advantage to modulate ebv-miR-BART3, however applicant has not demonstrated that any of the instantly recited sequences would in fact modulate ebv-miR-BART3 and affect viral titer during EBV lytic replication.

Applicant points to a declaration of Dr. Yitzhak Pilpel under 37 CFR 1.132 which asserts that the claimed nucleic acids would likely inhibit the expression of NP_039906.1 mRNA. However, the opinion declaration does not establish a credible utility of the instant sequences. The showings of the declaration are not commensurate in scope with the instant claims because the instant claims embrace a multitude of possible sequences that would not necessarily act through the ebv-miR-BART3 pathway and would not necessarily modulate ebv-miR-BART3 as asserted by the declaration.

Furthermore, there is an assumption that SEQ ID NO: 14051 actually is the product of the cleavage of the miRNA hairpin. Applicant has not demonstrated that expression of the miRNA hairpin or the single-stranded 22-mer would actually result in inhibition of NP_039906.1 mRNA. The data does not demonstrate that expression of the hairpin or the single-stranded SEQ ID NO: 14051.

The declaration sets forth that a nucleic acid sequence that is 18-25 nucleotides in length that is predicted by a miRNA target algorithm is likely to inhibit the expression of the protein encoded by that mRNA. It is important to note that the instant claims are not directed to any specific nucleic acid sequence that is 18-25 nucleotides in length and has been predicted by a miRNA target algorithm to act in any certain way, but embrace a huge genus of sequences of many lengths. It is the opinion of Dr. Pilpel that the sequences in column A would likely inhibit the expression of a protein encoded by the target gene in column B.

Cullen (Nature Genetics, Volume 37, Number 11, 2005, pages 1163-1165) teach that the miRNA biogenesis pathway includes three distinct RNA intermediates: the initial pri-miRNA transcript, the pre-miRNA hairpin, and the miRNA duplex and that all can be used as entry points to allow programming of RISC. Cullen teaches that this pathway can be entered with siRNA duplexes, shRNAs, or transcription of artificial pri-miRNA precursors, the third of which giving best results (see page 1164). Cullen teaches that data indicates that siRNAs that are expressed using the natural miRNA biogenesis pathway are more effective than those that are expressed by accessing downstream steps in the pathway, suggesting that miRNA biogenesis may be functionally coupled (i.e. each step may enhance the efficiency of subsequent steps (see page 1165).

Cullen et al. sets forth a schematic of the miRNA biogenesis pathway in Figure 1. There is no evidence that the instant genus of single-stranded sequences, as instantly claimed, would act in any manner in this pathway because the only step in the pathway that utilizes a single-stranded sequence is in RISC, wherein it appears to be necessary

for the miRNA to be in the form of a duplex to be able to load a single-strand into RISC. Therefore, applicant has not demonstrated that any nucleic acid comprised within SEQ ID NO: 399738, which is 7500 nucleotides in length, that comprises SEQ ID NO: 14051, which is 22 nucleotides in length, as well as a DNA encoding any of the sequences of this huge genus, as well as any sequence of any length that is at least 80% identical to any sequence of the huge genus or any DNA encoding any of the sequences, as well as the complement of any sequence of the huge genus, of any DNA encoding any of the sequences, or any of the sequences that are at least 80% identical to this genus would in fact initiate target inhibition via interacting with RISC, as the state of the art is such that the pri-miRNA is processed into a miRNA duplex and these processing steps are necessary for the resultant duplex to interact with RISC. Not only would the single-stranded sequences likely not interact with RISC, there is a high probability that the single-stranded sequences would be degraded by nucleases in the cell.

Currently, there is no evidence that a single stranded 22-mer, such as SEQ ID NO: 14051, as now claimed, which, if like most mature mRNAs, has at most 7 or 8 contiguous nucleotides complementary to the target gene, would regulate the target gene on its own if transfected or endogenously expressed as a single stranded 22-mer in the cell. Furthermore, it is unlikely that the instant sequences would act as single-stranded antisense oligonucleotides because these sequences do not have sufficient complementarity with the target that is required by single-stranded antisense oligonucleotides.

Applicant asserts that the utility is specific because the instantly recited sequences are disclosed as targeting a specific gene transcript. It is acknowledged that the instant specification discloses that the instant sequences have complementarity to a specific gene, but has not demonstrated any specific inhibitory effect thereof. The fact that the sequences have a degree of complementarity to a specific gene sequence does not establish utility. Although the specification correlates the sequences to a gene transcript, the specification does not correlate this to any specific, substantial, and credible utility.

Since the same can be done with any polynucleotide that is complementary to any gene sequence, the asserted utility is not specific. Also, because the specification does not disclose any specific function for the instant breadth of sequences, let alone SEQ ID NO: 399738 or 14051, aside from indicating that it may be expressed in certain cells or present in certain genomes, it is unclear how or why one of skill in the art would use the information obtained by measuring the expression of these sequences for any particular purpose aside from general research.

Furthermore, mismatches are known to alter the activity of the resultant miRNA sequence. Efficacy of a given miRNA is not strictly based upon complementarity of target sequence to the miRNA seed sequence, but rather depends upon other complementarity considerations as well, as evidenced by Mallory et al. (EMBO J, 2004, 23(16), pages 3356-3364). Mallory et al. teach that substitutions between the 5' and 3' regions of a miRNA reduced cleavage rates (see page 3360, for example). Therefore, it cannot be determined whether the instant breadth of sequences would act as asserted

by applicant without specific testing because applicant is asserting utility simply based upon algorithm predictions. Therefore, the asserted utility is not credible and is speculative.

Specific and substantial utility is thereby asserted based on bioinformatic data. The asserted utility has not been experimentally verified. Indeed, there is no experimental evidence of even a single biological function. Function is asserted solely on the basis of a computer program designed to predict miRNA-like hairpin sequences and mature miRNAs derived therefrom by Dicer-catalyzed processing, which information is mined from raw genomic sequences.

At issue, then, is whether one of skill would more likely than not believe the nucleic acids predicted by Applicant's algorithm, such as instant SEQ ID NOs: 399738 or 14051, as well as the remainder of the breadth of the sequences now claimed, would have the specific and substantial utility predicted by the program.

Though made by a proclaimed expert in the art, and containing sound scientific reasoning, the Declaration by Dr. Pilpel represents nothing more than an opinion. The declaration does not directly quantify the accuracy and/or false positive/false negative rate of the Inventor's algorithm, the program in question. The Declaration provides no experimental evidence validating either the predictive quality of the instant algorithm or the utility of the instantly claimed sequences. Such evidence if collected in a statistically relevant manner would be indicative of the accuracy of the algorithm.

The Declaration similarly fails to address the utility of the instant breadth of sequences. These sequences would clearly not be completely complementary to the

target mRNA. However, there is absolutely no evidence, beyond the algorithm, that the claimed miRNAs are biologically active in any manner, or even expressed by any cell. The question remains whether the bioinformatically predicted miRNAs now claimed would, more likely than not, have the utility asserted. The answer lies in the predictive quality of the program used to identify the miRNAs and their target sites. A quantifiable value is not readily apparent to the Examiner from the facts of record. Martin et al. (J. Biosci., 2007, 32, 1049-1052), reviewing the state of the art of miRNA prediction programs, state mammalian miRNA targets are considered difficult to predict because miRNA targets display only partial complementarity to the mature miRNA sequence (pg. 1049). Martin et al. further state that "Given the high level of both false-positives and false-negatives resulting from the application of current miRNA target prediction programs, it is clear that experimental testing of predicted miRNA targets is critically important in order to validate/confirm any putative miRNA-target gene combination" (pg. 1050, 4th complete paragraph). Martin et al. further teach that miRNA prediction programs rely on sequence, structure, and evolutionary conservation information to predict genes likely to be targeted by miRNAs, but that the requirement for conserved sites means that non-conserved sites, which may represent real targets, are completely missed.

Smalheiser et al. (Methods Mol. Biol., 2006, 34, pages115-127) in an article entitled "Complications in miRNA Target Prediction" state that complementarity between miRNAs and their targets is not the only factor that may govern which miRNA-mRNA target interactions are effective in vivo. One must consider the potential importance of

mRNA target secondary structure, as well as the strong possibility that RNA-binding proteins may participate in miRNA recognition. Furthermore, both miRNA and mRNA need to be coexpressed in proper amounts within the cell for effective interaction to occur, and A-to-I editing of RNA might abrogate potential mRNA targets from being effectively silenced by the RNA-induced silencing complex (page 124). Smalheiser et al. further teach that not all mammalian miRNAs interact with their targets via "short seeds," complementary regions of 6-8 nucleotides, but, instead, may interact via "long" seeds and perfect matches (page 115-6), and because new miRNAs are constantly being discovered this list of binding determinants may not be complete. Thus, multiple factors are involved in miRNA-target binding and recognition.

Thus, in view of the totality of the evidence, one of skill would have reason to doubt the objective truth of the asserted utility. While the instant algorithm provides a list of putative miRNAs and corresponding target sites, there is reason to question whether the bioinformatic algorithm used to produce this list correctly identifies an miRNA and its function (i.e., at least one biological function) with minimally acceptable false positive and false negative rates such that one of skill would believe the miRNA would, more likely than not, inhibit the gene predicted by the software. Without experimental validation or any verifiable evidence of the accuracy and error rates of the instant program, and in view of the state of the art at the time of invention, one of skill would reasonably question the certainty of the prediction at the time of filing. The skilled artisan would be led to believe only that the instantly claimed nucleic acids require further research to verify the asserted utility.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16, 18, 22, 25, 26, and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35, 47, 48, and 51 of copending Application No. 10/536,560. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of application '560 are directed to isolated nucleic acid sequences that overlap in scope. For example, SEQ ID NOs: 1194 (69-mer) and 775 (101-mer) each comprise instant SEQ ID NO: 14051 and thus the sequences are obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requests for the rejection to be held in abeyance until there is allowable subject matter.

New Objections/Rejections

Claim Objections

Claim 25 is objected to because of the following informalities: Claim 25 does not end with a period. Appropriate correction is required.

Claims 16, 22, and 26 are objected to because of the following informalities: Claim 16 recites non-elected subject matter (the subject matter of part (a) that is not directed to SEQ ID NO: 14051) that has been withdrawn from consideration, as explained above. Claims 22 and 26 are objected to because they depend from claim 16. Appropriate correction is required. It is noted that claims 18, 25, and 28 are not objected to because claim 18 limits the subject matter of part (a) of claim 16 to SEQ ID NO: 14051.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 18, 22, 25, 26, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The amended claims are directed to an isolated nucleic acid wherein SEQ ID NO: 399738 comprises the nucleic acid and wherein the nucleic acid comprises SEQ ID NO: 14051; a DNA encoding SEQ ID NO; 14051 or any sequence comprised within SEQ ID NO: 399738 that comprises SEQ ID NO: 14051; a sequence of any length that is at least 80% identical to any sequence comprised within SEQ ID NO: 399738 that comprises SEQ ID NO: 14051 or to a DNA encoding SEQ ID NO; 14051 or any sequence comprised within SEQ ID NO: 399738 that comprises SEQ ID NO: 14051; or the complement of any of the above.

However, the specification does not contemplate each of the above limitations that were newly introduced into the claims filed on 5/21/08. In applicant's arguments filed 5/21/08, applicant asserts that support can be found in Table 1, line 30685, Table 2, lines 1635432, 1635101, 1634771, 1634991, and 1634881, sequence listing, claim 1, and paragraphs 0045, 0048, 0052, and 0054. However, upon review of the specification, tables, and sequence listing, and particularly at the locations pointed to by applicant, support cannot be found for the instant genus.

Support is not evident for the instant genus of molecules that embrace any nucleic acid comprised within SEQ ID NO: 399738, which is 7500 nucleotides in length, that comprises SEQ ID NO: 14051, which is 22 nucleotides in length. Therefore, the claims embrace any sequence within the 7500-mer that comprises the 22-mer, as well as a DNA encoding any of the sequences of this huge genus, as well as any sequence of any length that is at least 80% identical to any sequence of the huge genus or any DNA encoding any of the sequences, as well as the complement of any sequence of the huge genus, of any DNA encoding any of the sequences, or any of the sequences that are at least 80% identical. Support is not evident for this huge genus of sequences at the locations of the specification, tables, and sequence listing pointed to by applicant.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

Furthermore, there is no support for each of the newly added claim limitations in the claimed priority documents. Therefore, the effective filing date of the instant claims

is considered, for purposes of prior art, to be 4/2/04, which is the filing date of the instant application.

A review of the specification, and particularly at the pages pointed to by applicant, does not reveal support for where the various claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 5/21/08.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16, 18, 22, 25, 26, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang (US 2002/0198371 A1).

The instant claims are directed to an isolated nucleic acid wherein SEQ ID NO: 399738 comprises the nucleic acid and wherein the sequence of the nucleic acid comprises a sequence with the structural characteristics recited in claim 16, as well as a vector or probe comprising the sequence.

Wang teaches a 522 nucleotide sequence that comprises the DNA equivalent of instant SEQ ID NO: 14051 (see SEQ ID NO: 184374 of Wang and sequence search result #12 in the search results titled "20070814_160752_us-10-708-952b-

14051.rnpbm" in SCORE). The nucleotide sequence of Wang comprises a sequence that is at least 80% identical to instant SEQ ID NO: 14051. Even taking into consideration the 4 DNA bases of Wang et al., the 22-mer portion of the sequence is 81.8% identical to instant SEQ ID NO: 14051. The instant claims do not recite any length limitation. Furthermore, the claims require for SEQ ID NO: 399738 to comprise the nucleic acid. Although SEQ ID NO: 399738 does not comprise the full 522-mer of Wang, SEQ ID NO: 399738 comprises SEQ ID NO: 14051, which is the only requirement of the instant claims. The instant claims do not require for SEQ ID NO: 399738 to comprise the full nucleotide sequence, but rather to comprise SEQ ID NO: 14051, as SEQ ID NO: 399738 could not comprise the requirements of parts (b)-(d), as SEQ ID NO: 399738 is a RNA. Therefore, the sequence of Wang et al., which comprises a sequence that is at least 80% identical to (a) (SEQ ID NO: 14051) plus additional nucleotide sequence meets the structural limitations of the instant claims. Furthermore, Wang teaches SNP probes complementary to the disclosed sequences as well as vectors comprising such. The instant specification does not define the term vector and therefore any carrier or transporter would meet the instant limitation of a vector. For example, the long sequence of Wang which comprises the shorter fragment meets the instant limitation of being a vector comprising the short sequence.

Therefore, the instant claims are anticipated by Wang.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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